Women's Heart Health along the lifecourse

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Leiden December 7th - 2023

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Disclosure of speaker's interests

(Potential) conflict of interest	None/See below
Potentially relevant company relationships in connection with event	**Company names:**
Sponsorship or research funding	
Fee or other (financial) payment	Omron, Organon, Novartis
Shareholder	
Other relationship, i.e. …	

THE LANCET

Sept 2021

"Historically, the anatomy and physiology of bodies with vaginas have been neglected."

See *Perspectives* page 1124

The NEW ENGLAND JOURNAL of MEDICINE

Debra Malina, Ph.D., *Editor*

Medicine Is Not Gender-Neutral — She Is Male

Kiki M.J. Lombarts, Ph.D., and Abraham Verghese, M.D.

March 2022

Roles Go Back to Ancient Greece.

Women Are Still Paying the Price Today

2022 NPO Doc **Reference man**

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Gendered Innovations | Stanford University

Chronic Pain: Analyzing How Sex and Gender Interact

Colorectal Cancer: Analyzing How Sex and Gender Interact

Covid-19: Analyzing Sex and Analyzing Gender

De-Gendering the Knee: Overemphasizing Sex Differences as a Problem

Dietary Assessment Method: Analyzing How Sex and Gender Interact

Gender-Related Variables for Health Research

Heart Disease in Diverse Populations

Medical Technology: Intersectional Approaches

Nanomedicine: Analyzing Sex

Prof Londa Schiebinger, History Science Stanford University

Nanotechnology-Based Screening for HPV: Rethinking Research Priorities

Nutrigenomics

Osteoporosis Research in Men: Rethinking Standards and Reference Models

Prescription Drugs: Analyzing Sex & Gender

Systems Biology: Analyzing How Sex and Gender Interact

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1. Chronic inflammatory diseases such as endometriosis are associated with a higher CVD risk

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3. **The onset of hypertension during menopause transition is asymptomatic**

1. Chronic inflammatory diseases such as endometriosis are associated with a higher CVD risk

2. 40% of women with preeclampsia/HELLP in pregnancy already have hypertension by the age of 40

3. The onset of hypertension during menopause transition is asymptomatic

4. Determining the coronary calcium score with CT (CAC score) can be a tool to assess whether it is safe to give MHT

Cardiovascular disease is the leading cause of mortality in women

Total Deaths in Women in USA 2016: 1,236,003
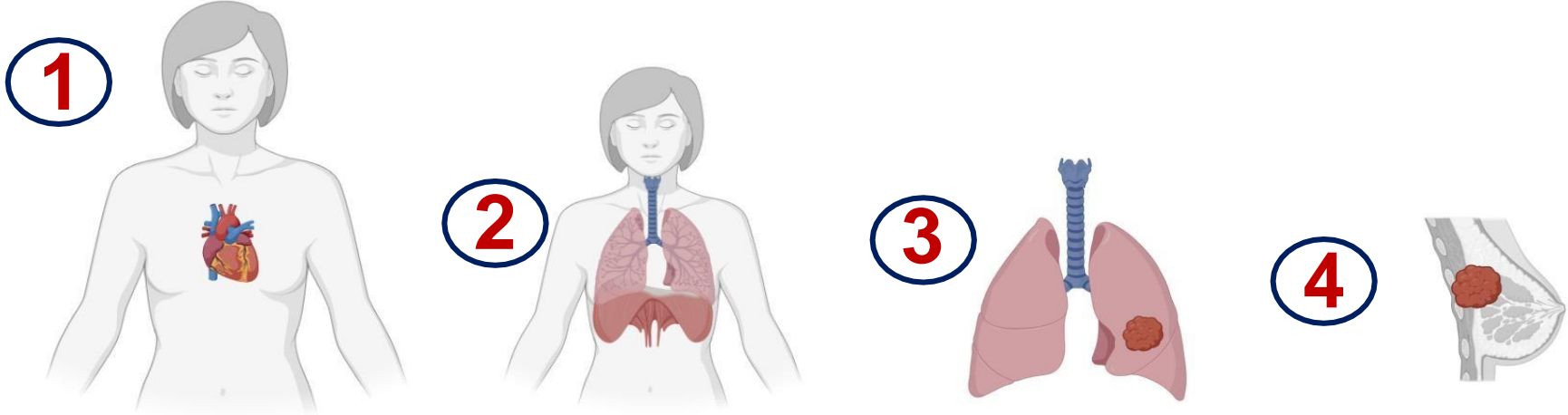
Cardiovascular disease 412,244 deaths	Chronic Lung Disease 81,551 deaths	Lung Cancer 70,500 deaths	Breast Cancer 40,920 deaths

Benjamin EJ et al., Circulation 2019

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Oestrogen levels in Women

AGE

ESTROGENS

ERα   ERβ   GPER-1

endothelial cells

Promotion of vasodilation

Protection of barrier integrity

Reduction of inflammation

Promotion of endothelium healing

Promotion of angiogenesis

Reduction of LDL transport

Reduction of apoptosis

Promotion of proliferation

Promotion of migration

Sex hormones dysfunction and CVD risk:

PCOS, POF: sex hormones dysfunction in fertile age

Menopause: Exhaustion of ovarian function

↓ E2
↑Androgen Levels
(↓ SHBG)

Compensatory hyperinsulinemia

Hyperandrogenism

Insulin Resistance

Oxidative stress

Pro-atherogenic dyslipidemia
Fibrinolysis
Hyperfibrinogenemia
Hyper-coagulability

Pro-inflammatory state / Sub-clinical Inflammation

Change in body fat distribution

Visceral adiposity (Higher leptin, lower adiponectin)

↓ Insulin sensitivity

VASCULAR EFFECTS
↑ Vascular peripheral resistance/↓ Vascular compliance
↑ Carotid IMT, Endothelial dysfunction
↑ Renin –Angiotensin system and natriuretic peptides

↓ Cardiac vagal modulation
↑ Sympathetic activity

Hypertension

Glucose intolerance
T2DM
Obesity
Metabolic syndrome

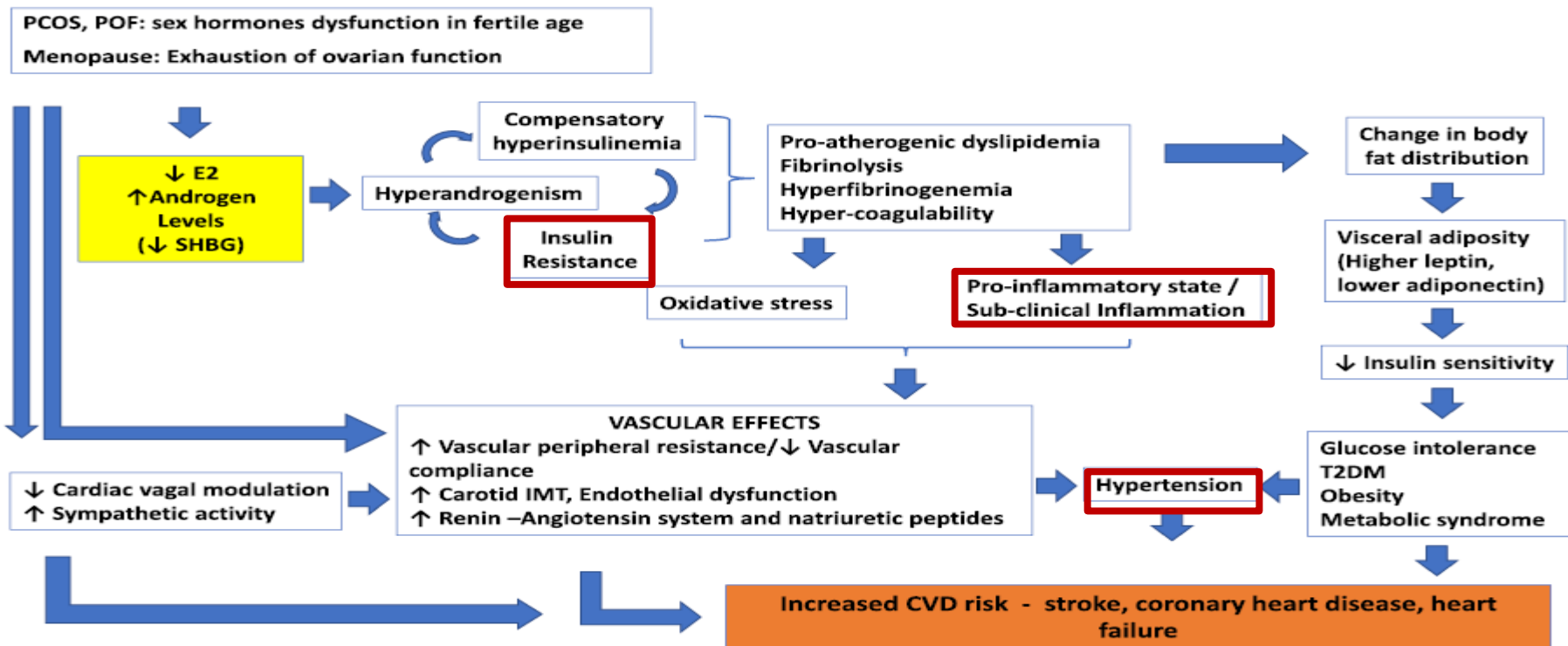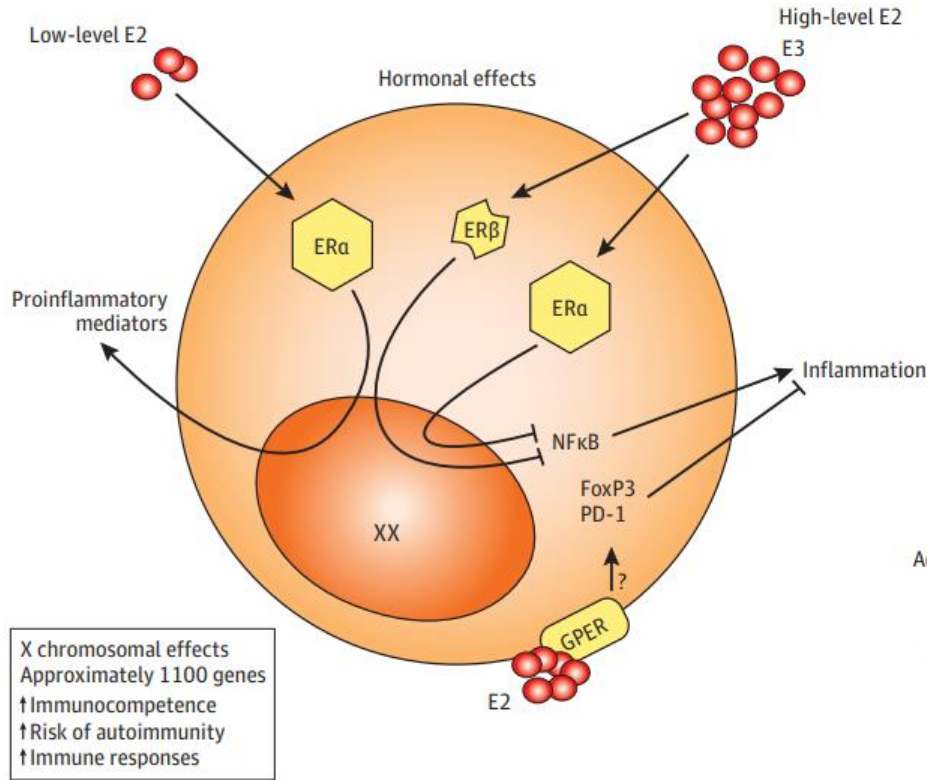Increased CVD risk - stroke, coronary heart disease, heart failure

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Figure 3. Interaction of Hormones by Sex With the Immune System

A Female immune cell

Low-level E2

High-level E2 E3

Hormonal effects

ERβ

ERα

ERα

Proinflammatory mediators

Inflammation

NFκB

FoxP3 PD-1

XX

GPER

?

E2

X chromosomal effects
Approximately 1100 genes
↑Immunocompetence
↑Risk of autoimmunity
↑Immune responses

B Male immune cell

Testosterone

Hormonal effects

AR

Ptpn1 —| T_H1 response

Adaptive immunity

XY

CD4+FoxP3+ T regs
Innate immunity

Y chromosomal effects
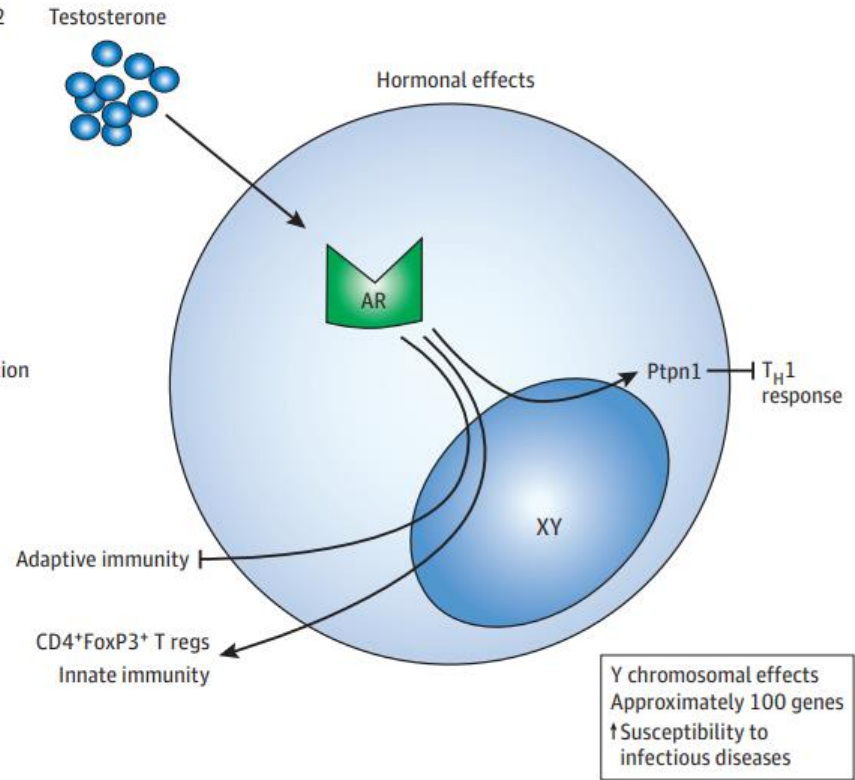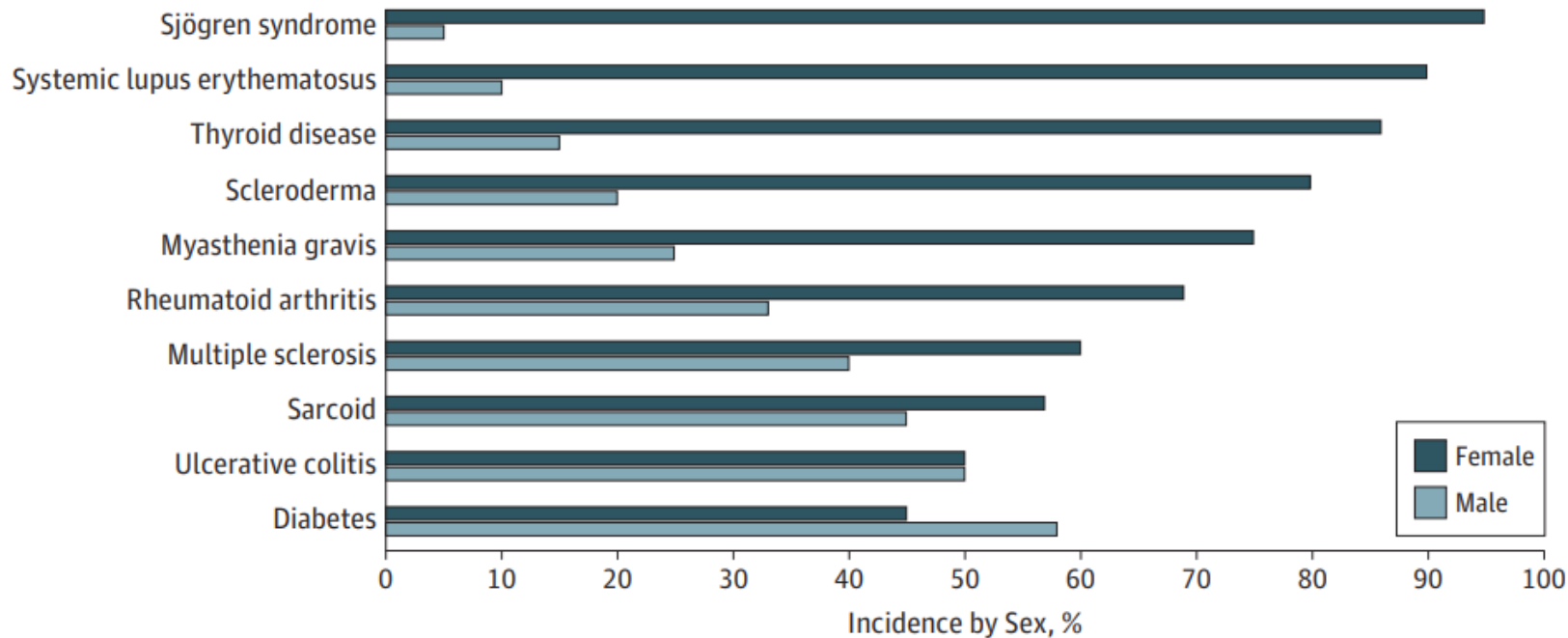Approximately 100 genes
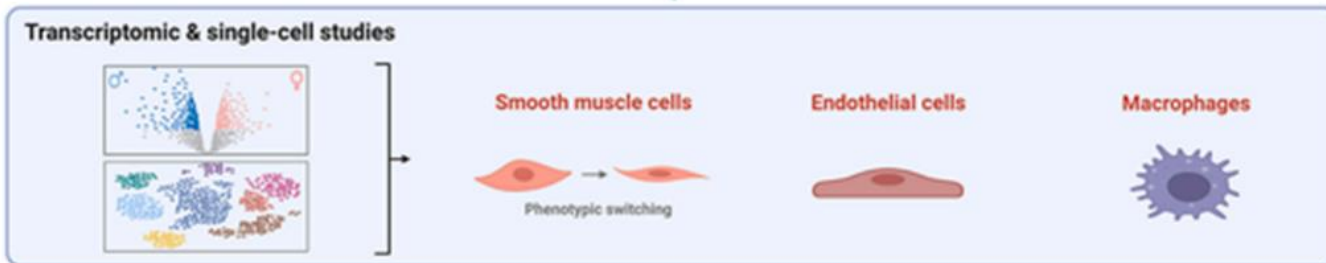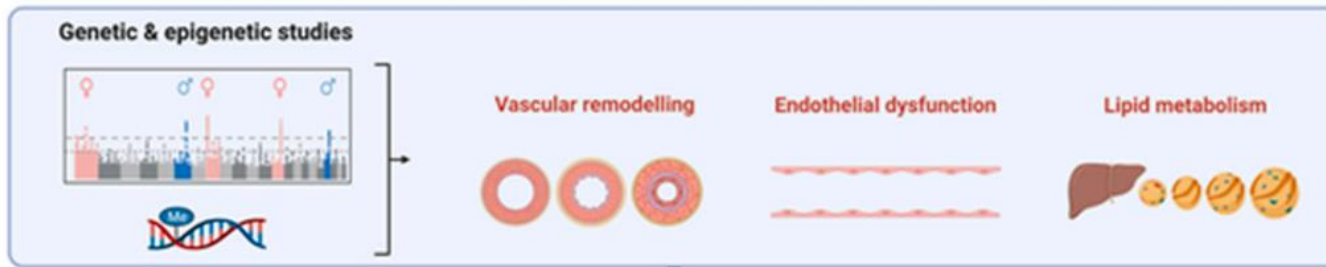↑Susceptibility to infectious diseases

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Figure 2. Distribution of Major Autoimmune Diseases by Sex

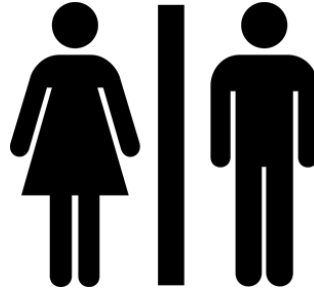Radboudumc

Sex differences in CAD

Fibrous plaque ♀ — **Atheromatous plaque** ♂

Known sex differences in plaque biology

Genetic & epigenetic studies
Vascular remodelling — Endothelial dysfunction — Lipid metabolism

Transcriptomic & single-cell studies
Smooth muscle cells — Phenotypic switching — Endothelial cells — Macrophages

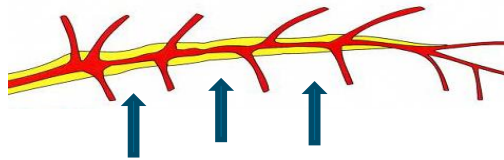Sakkers TR et al.
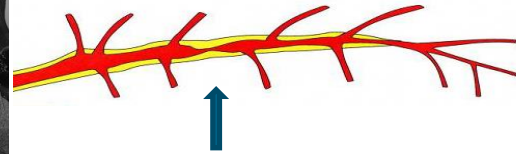Atherosclerosis 2023

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Spasm in the epicardial and microvasculature of the coronary arteries
(80% women)

Stenoses in the epicardial coronary arteries
(80% men)

Diffuse atherosclerosis

Focal stenosis

WOMEN'S HEARTS ≠ MEN'S HEARTS

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Woman 46 yrs, since 4 yrs misunderstood symptoms of chest pain. After 3 CAGs sent to a psychiatrist …

Spasm at infusion 2 µgr Acetylcholine

after nitro

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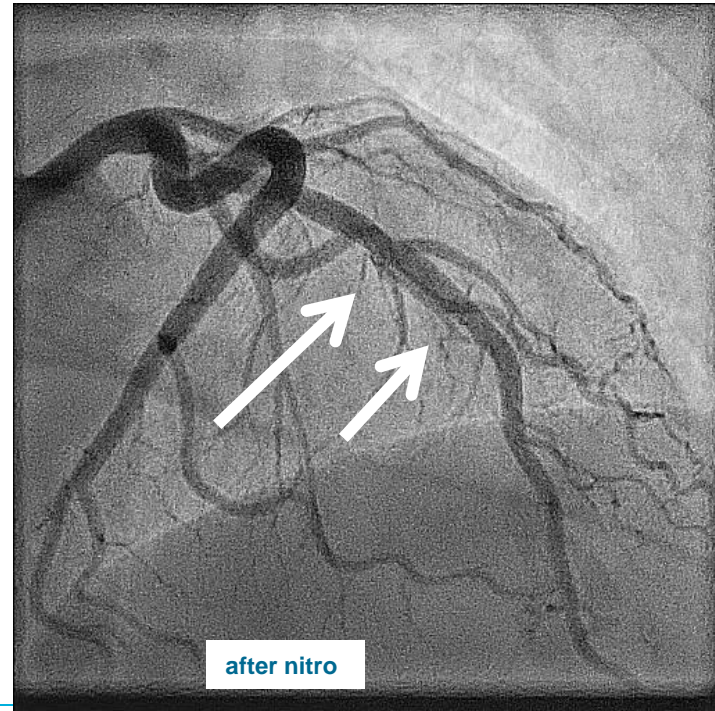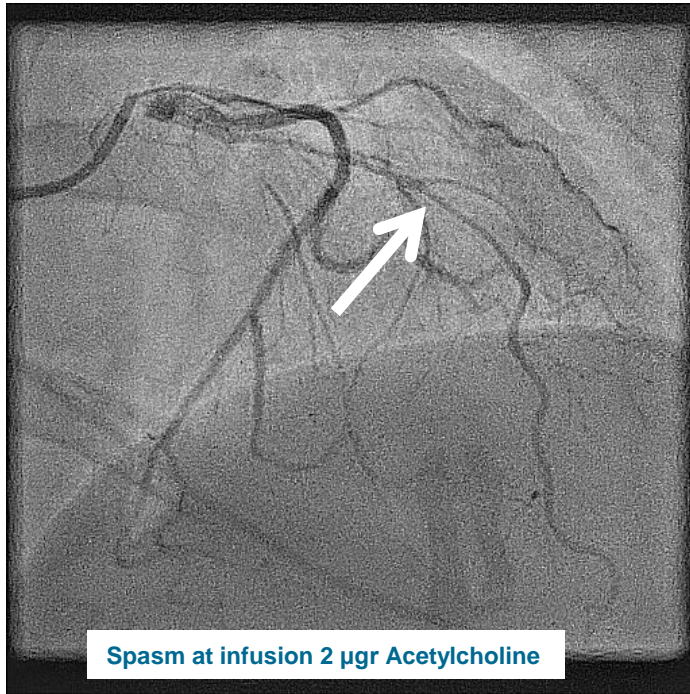
Are symptoms in women 'atypical'??

- fluctuating pain
- at rest & exercise
- shortness of breath
- extreme tiredness
- role mental stress

No, symptoms are ***characteristic*** for the underlying disease

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Female representation in cardiology trials over time

A Global attributable deaths from Level 2 risk factors for females in 2019

Risk factors (top to bottom):
- High systolic blood pressure
- Dietary risks
- High fasting plasma glucose
- Air pollution
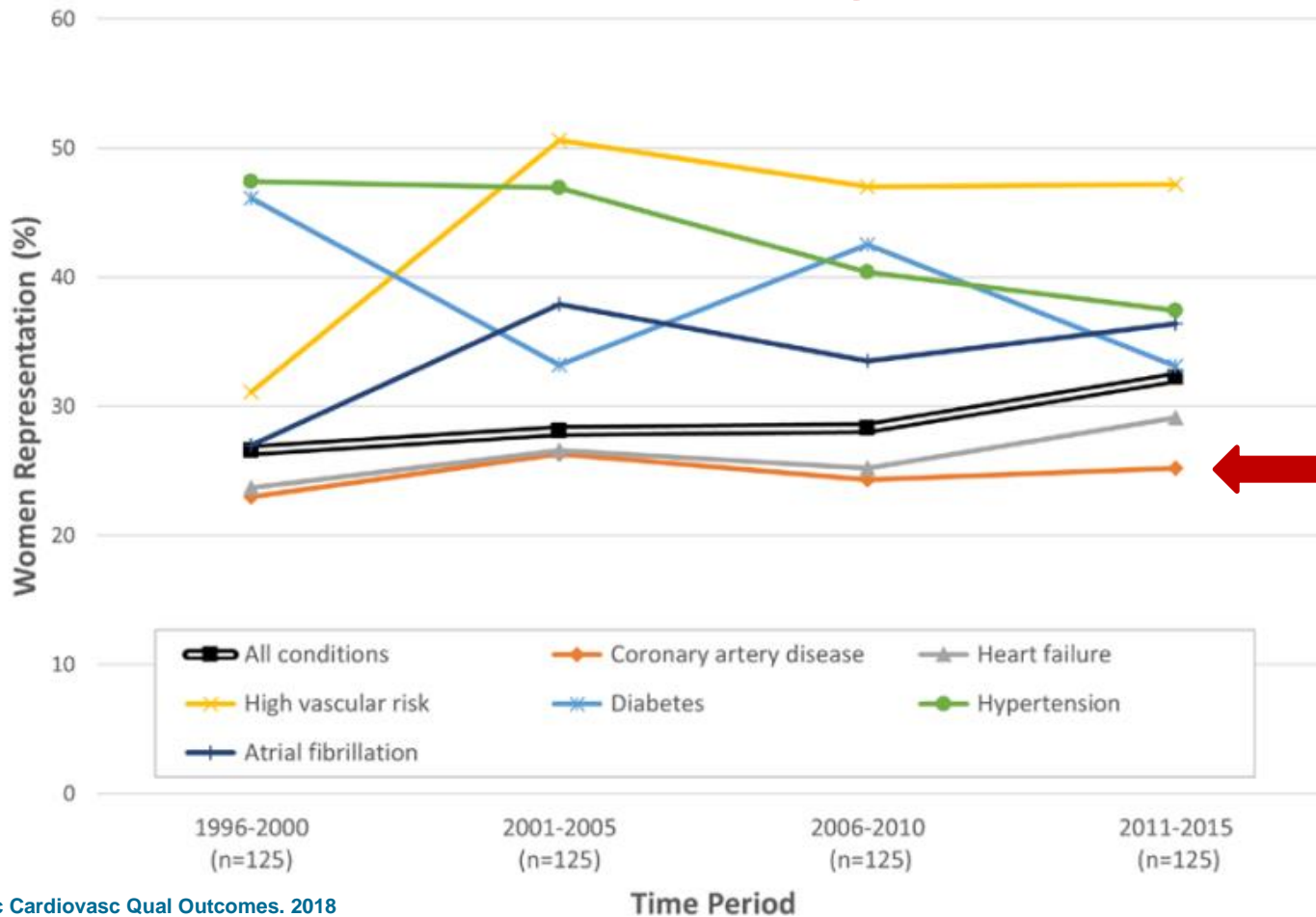- High body-mass index
- Tobacco
- High LDL cholesterol
- Kidney dysfunction
- Child and maternal malnutrition
- Non-optimal temperature
- Unsafe water, sanitation, and handwashing
- Unsafe sex
- Low physical activity
- Alcohol use
- Other environmental risks
- Occupational risks
- Low bone mineral density
- Drug use
- Intimate partner violence
- Childhood sexual abuse and bullying

Report Global Burden Disease Lancet 17 October 2020

Legend:
- Cardiovascular diseases
- Chronic respiratory diseases
- Diabetes and kidney diseases
- Digestive diseases
- Enteric infections
- HIV/AIDS and sexually transmitted infections
- Maternal and neonatal disorders
- Musculoskeletal disorders
- Neoplasms
- Neurological disorders
- Nutritional deficiencies
- Other infectious diseases
- Other non-communicable diseases
- Respiratory infections and tuberculosis
- Self-harm and interpersonal violence
- Substance use disorders
- Transport injuries
- Unintentional injuries

HYPERTENSION SIGNS AND SYMPTOMS

Fainting · Dizziness · Low blood pressure · Irregular Heartbeat · Fatigue · Vomiting · Nausea

Symptomatic hypertension is often interpreted as menopause

- **fatigue, lack of energy**
- **continuous chest pain : 'bra feels too tight'**
- **pain between shoulder blades**
- **fluid retention : ankles, stomach, hands, eyelids etc**
- **palpitations, PAF**
- **shortness of breath**
- **sweating, hot flushes**
- **insomnia**
- **headaches, dizzyness**

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General risk factors in women
- Obesity *
- Diabetes*
- Hypertension*
- Dyslipidaemia
- Age
- Inactivity
- Family history
- Smoking*

Risk Factors in Young women
- Pre-eclampsia
- Gestational diabetes
- PCOS;endometriosis
- Oral contraceptive pill use
- Functional hypothalamic amenorrhea
- Autoimmune conditions
- Psychosocial risks such as depression and stress
- Breast cancer therapy

Risk factors in middle age women
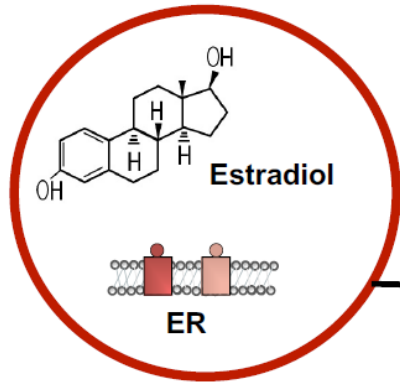- Pre-menopause
- Early menopause
- **Vasomotor symptoms +++**
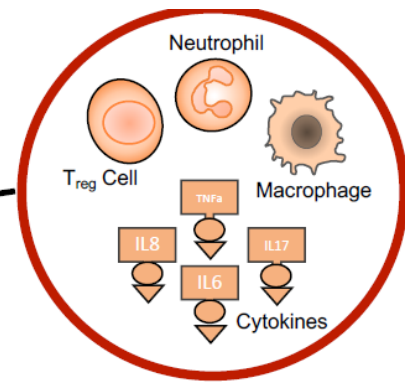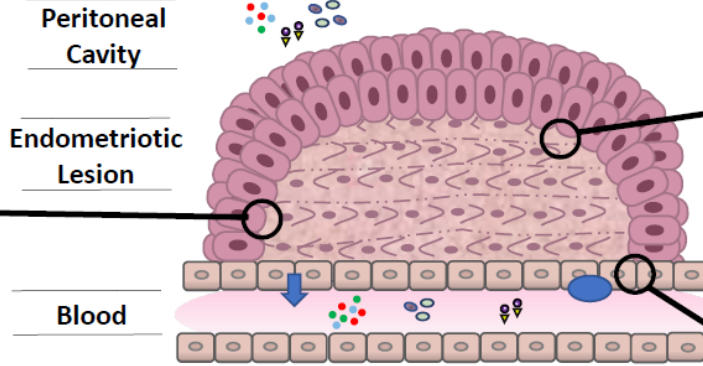
Risk factors in older women
- Post-menopausal

Excess CVD morbidity and mortality
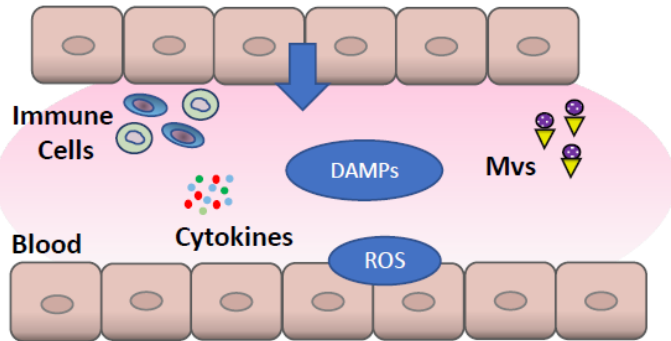
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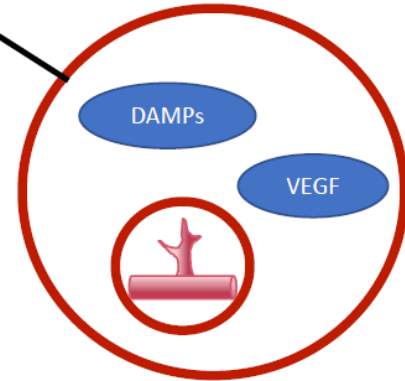
Meta-analysis endometriosis and CVD risk:

Forest plot showing HR with 95% CI and Weight (%) by Study.

Study	HR with 95% CI	Weight (%)
Ischemic heart disease		
Mu 2016	1.62 [1.39, 1.89]	36.1
Okoth 2021	1.40 [1.22, 1.61]	43.9
Wei 2021	1.52 [1.24, 1.87]	20.0
Heterogeneity: I^2 = 11.79%, H^2 = 1.13	1.50 [1.36, 1.66]	
Heterogeneity: Chi2 = 1.91, p = 0.38		
Overall effect: p < 0.001		
Cerebrovascular disease		
Chiang 2021	1.16 [1.02, 1.31]	44.0
Farland 2021	1.34 [1.10, 1.62]	18.0
Okoth 2021	1.19 [1.04, 1.36]	38.0
Heterogeneity: I^2 = 0.01%, H^2 = 1.00	1.20 [1.11, 1.30]	
Heterogeneity: Chi2 = 1.49, p = 0.48		
Overall effect: p < 0.001		

Risk of CV disease - Endometriosis (1.00 – 2.00)

Poeta do Couto C et al. Maturitas 2023;171:45-52.

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11 Febr 2022: socio-economic impact of endometriosis

Steps to Reduce Delayed & Missed Cardiovascular Disease Diagnosis in Women

- Stop Stigmatizing Women with Symptoms — STOP
- Empower Women to Advocate for Their Health
- Recognize & Consider SDOH
- Use Trustworthy Patient Education Resources
- Increase Research on CVD in Women
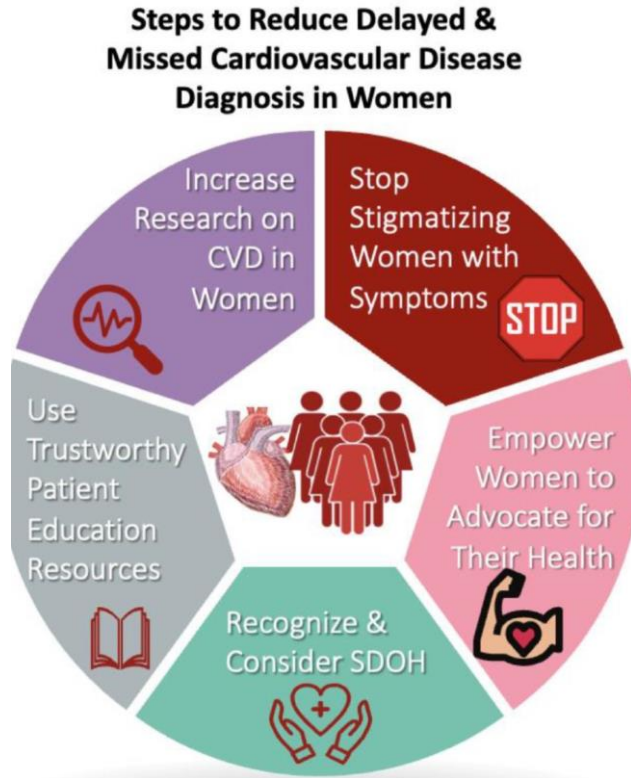
Emmanuel Macron
@EmmanuelMacron
Officiel du gouvernement - France

L'endométriose.
Ce n'est pas un problème de femmes, c'est un problème de société. La stratégie nationale que nous lançons porte l'espoir d'une meilleure qualité de vie pour des millions de filles et de femmes.
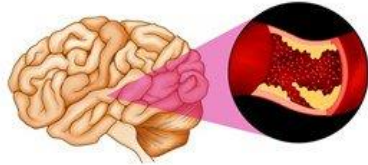
Translate Tweet

5:33 | 807.5K views

Hypertensive Disorders of Pregnancy

Chronic hypertension
370% increase

Coronary heart disease
250% increase

Stroke
81% increase

All-cause death
50% increase
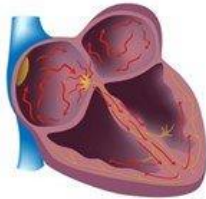
Atrial arrhythmias
50% increase
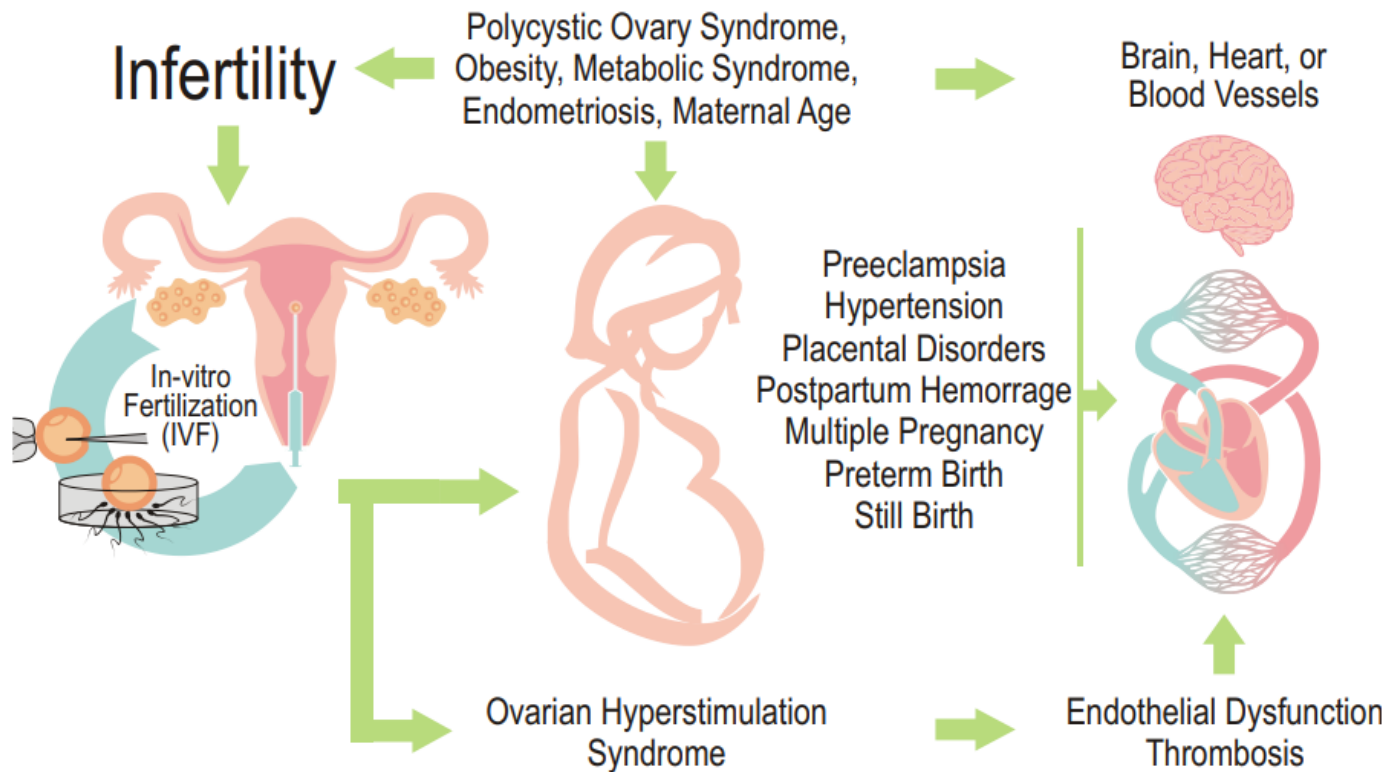
Heart failure:
400% increase

Cardiovascular death
221% increase

Coutinho T et al. Curr Treat Options Cardiovasc Med. 2018

udumc

Concept linking infertility subtypes, infertility treatment, pregnancy outcome, and longer-term cardiovascular health:

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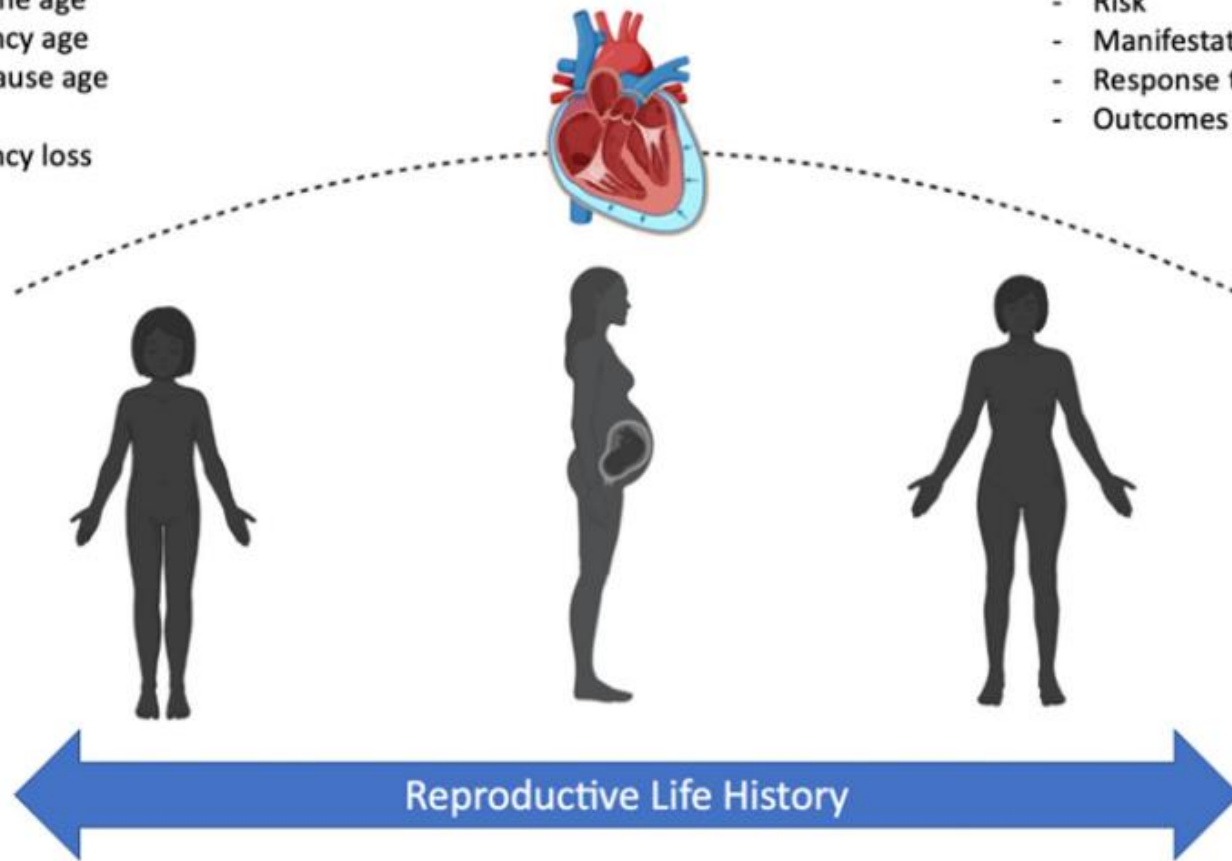
HF = heart failure.

CENTRAL ILLUSTRATION: Female Reproductive Factors and Risk of New-Onset Heart Failure: Findings From UK Biobank

Female reproductive factors that increase heart failure risk

N = 229,026

- Younger age at menarche **< 12 yrs**

- Younger maternal age at first live birth **< 21 yr**
  Younger maternal age at last live birth **< 26 yrs**
  Larger number of live births **> 4 children**
  Stillbirth **20-43% higher risk HF**

- Younger age at menopause **< 45 yrs**
  Shorter reproductive lifespan

.umc
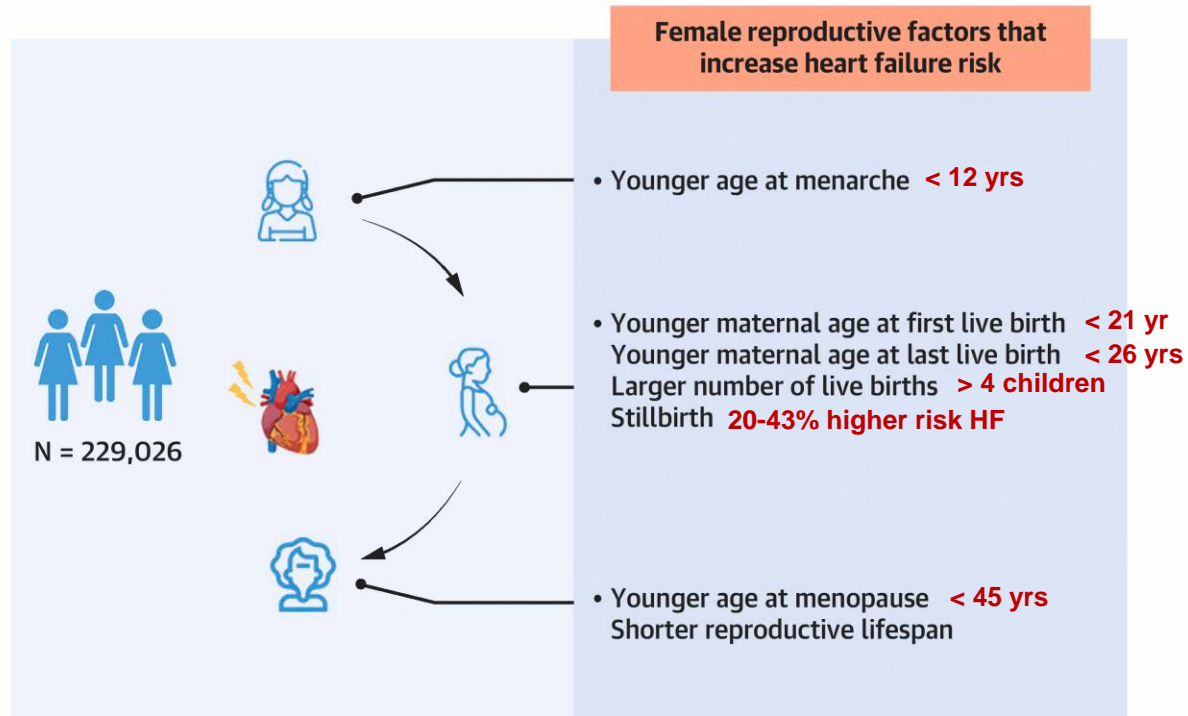
CAC score with CT can be helpful to assess individual CVD risk

Coronary artery calcium test for heart disease risk assessment

Cholesterol plaque buildup can block coronary arteries in the heart, increasing the risk of myocardial infarction (or heart attack). Coronary artery calcium (CAC) in the plaques can be seen and measured on a computed tomography (CT) scan to help guide assessment and treatment of those at risk for heart disease.

Plaque with CAC

CORONARY ARTERY

CAC

HEART

VIEW OF HEART ON CT SCAN

Other factors are also considered when assessing heart disease risk
- Cholesterol levels
- Blood pressure
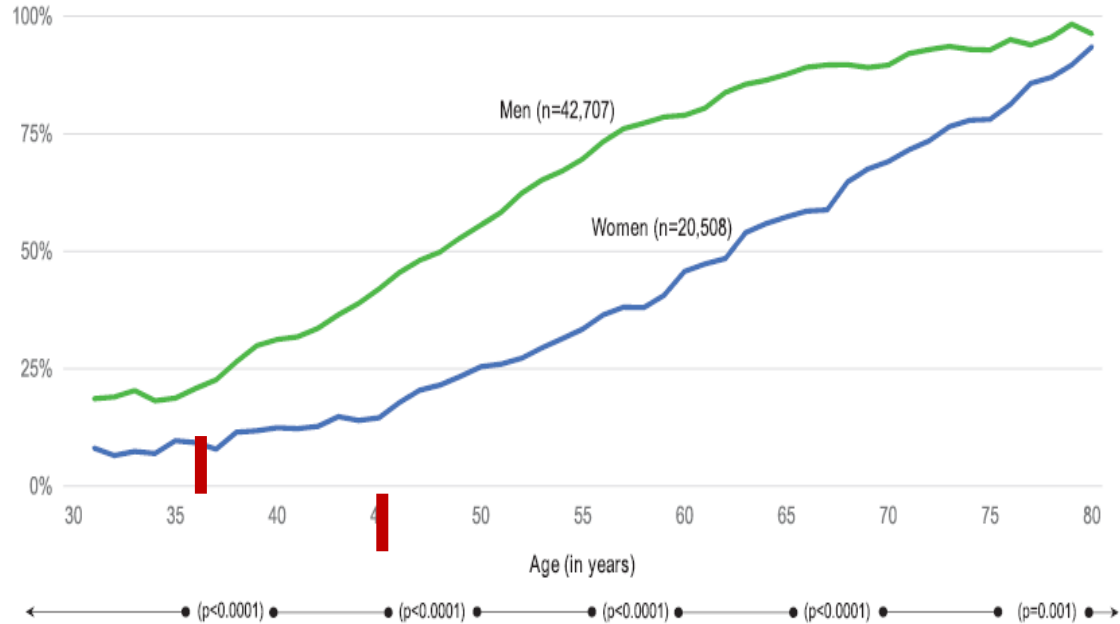- Diabetes
- Body weight
- Age, sex, and family history
- Cigarette smoking
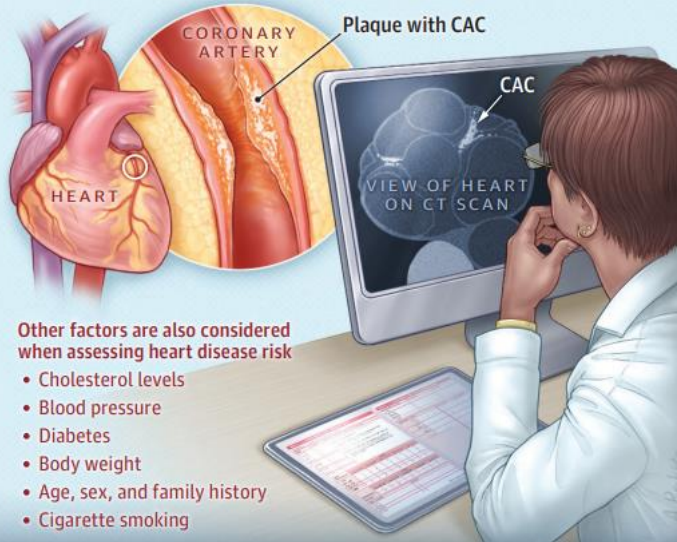
CAC score with CT scan in men/women over lifetime:

Men (n=42,707)

Women (n=20,508)

Age (in years)

(p<0.0001)   (p<0.0001)   (p<0.0001)   (p<0.0001)   (p=0.001)

1/3 of women after PE has CAC > 0 at 50 years of age

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Cardiovascular Risk Assessment

Traditional Risk Factors:
- Hypertension
- Dyslipidemia
- Diabetes
- Obesity
- Smoking
- Sedentary lifestyle
- Family history
- Poor diet
- Environmental pollution

Pregnancy-Related Risk Factors:
- Preeclampsia
- Gestational hypertension
- Gestational diabetes
- Preterm delivery
- Delivery of small for gestation age infant
- Recurrent spontaneous pregnancy loss

Other Female-Specific Factors:
- Early menarche
- Premature menopause
- Hormone-based contraception
- Polycystic ovarian syndrome
- Autoimmune disorders
- Chronic inflammatory conditions
- Depression and other mental health conditions

Social Determinants of Health · Cultural Issues and Norms · Language and Health Literacy

Race and Ethnicity Contribution

Heterogeneity within each of these populations resulting in variation in risk factors and CVD impact

Underrepresentation in treatment trials and as a result inadequate data on optimal treatments to reduce CVD risks
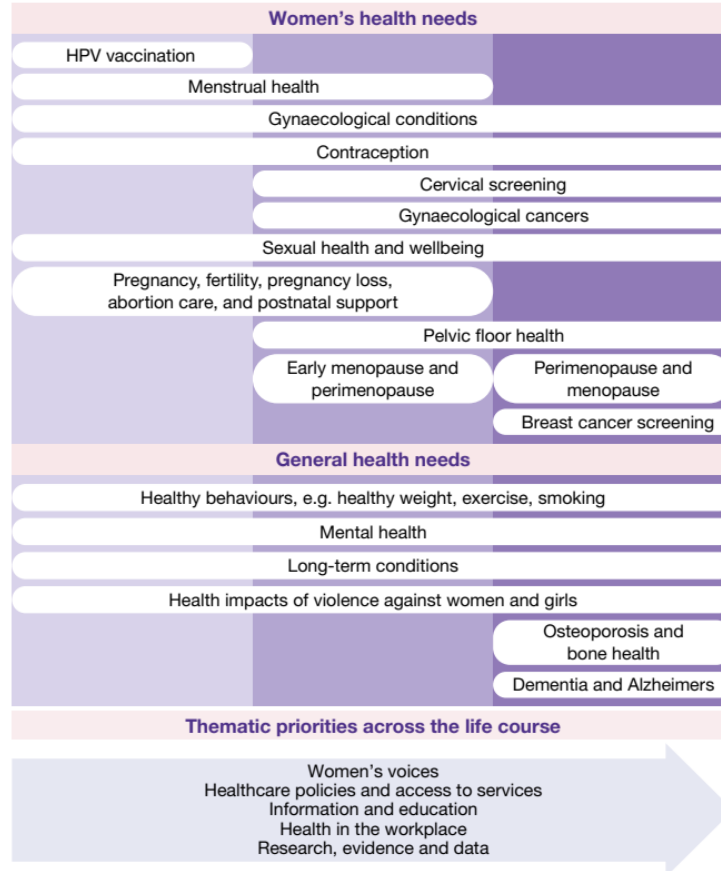
A WOMAN'S HEART
Why female heart health really matters
DR ANGELA MAAS
WORLD-RENOWNED EXPERT IN FEMALE CARDIOLOGY
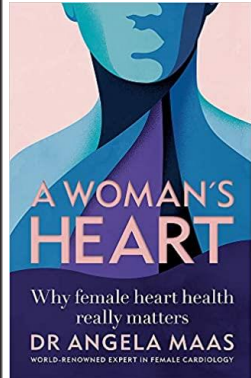
Department of Health & Social Care

Women's Health Strategy for England

Published August 2022

CP 736

Women's health across the life course

	ADOLESCENTS AND YOUNG ADULTS PUBERTY-24	MIDDLE YEARS 25-50	LATER YEARS 51+
Women's health needs			
HPV vaccination			
Menstrual health			
Gynaecological conditions			
Contraception			
Cervical screening			
Gynaecological cancers			
Sexual health and wellbeing			
Pregnancy, fertility, pregnancy loss, abortion care, and postnatal support			
Pelvic floor health			
Early menopause and perimenopause		Perimenopause and menopause	
			Breast cancer screening
General health needs			
Healthy behaviours, e.g. healthy weight, exercise, smoking			
Mental health			
Long-term conditions			
Health impacts of violence against women and girls			
			Osteoporosis and bone health
			Dementia and Alzheimers

Thematic priorities across the life course

Women's voices
Healthcare policies and access to services
Information and education
Health in the workplace
Research, evidence and data

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FACT SHEET: President Joe Biden to Announce First-Ever White House Initiative on Women's Health Research, An Effort Led by First Lady Jill Biden and the White House Gender Policy Council

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Interesse in Women's Health?

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- Hester den Ruijter (h.m.denruijter-2@umcutrecht.nl)
- Carmen van Vilsteren (c.f.m.v.vilsteren@tue.nl)